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In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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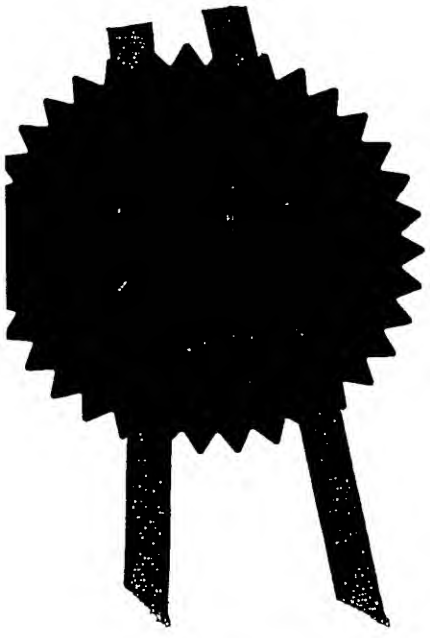

Signed

Dated 6 August 2004

Patents Form 1/77

Patents Act 1977
(Rule 16)

The Patent Office

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — SMC 60613/GB/P2

2. Patent application number *(The Patent Office will fill in this part)* — 0406760.9 — 2 6 MAR 2004

3. Full name, address and postcode of the or of each applicant *(underline all surnames)* — Avecia Limited
Hexagon House
Blackley
Manchester, M9 8ZS

Patents ADP number *(if you know it)* — 07764137001

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — Process and Compounds

5. Name of your agent *(if you have one)* — GAIRNS, Raymond Stevenson

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* — Avecia Limited
Hexagon House
PO Box 42
Blackley
Manchester M9 8ZS

07764137001

Patents ADP number *(if you know it)* — ~~69334720001~~ 94

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

See note (d))

12:01 70/ 92 5268600

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	5
Claim(s)	4
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	Cover Page

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 26-3-04

Avecia Limited Authorised Signatory

12. Name and daytime telephone number of person to contact in the United Kingdom

K.M.Pinder/G.Terry 0161 721 1361/2

Warning

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Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *If you have answered 'Yes' Patents Form 7/77 will need to be filed.*

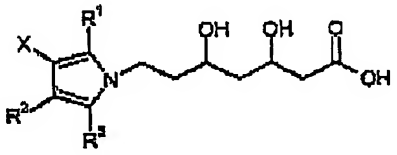
e) *Once you have filled in the form you must remember to sign and date it.*

f) *For details of the fee and ways to pay please contact the Patent Office.*

PROCESS AND COMPOUNDS

The present invention concerns a process and intermediate compounds useful in the preparation of statins, particularly atorvastatin.

According to the present invention, there is provided a process for the preparation of a compound of formula (7):



wherein

R^1 represents an alkyl group, such as a C_{1-6} alkyl group, and preferably an isopropyl group;

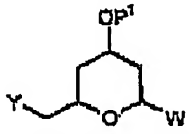
R^2 represents an aryl group, preferably a phenyl group

R^3 represents an aryl group, preferably a 4-fluorophenyl group

X represents a group of formula $-COZ$, wherein Z represents $-OR^4$, in which R^4 represents an alkyl, preferably a methyl or ethyl, group, or $-NR^5R^6$, wherein R^5 and R^6 each independently represent H, alkyl, or aryl, and preferably R^5 is H and R^6 is phenyl

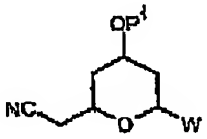
which comprises

a) cyanating a compound of formula (1):

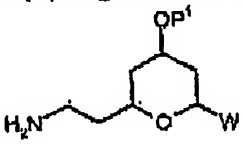


wherein Y represents a halo group, preferably Cl or Br; P^1 represents hydrogen or a protecting group, and W represents =O or $-OP^2$, in which P^2 represents hydrogen or a protecting group,

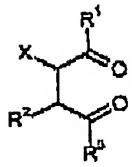
to give a compound of formula (2):



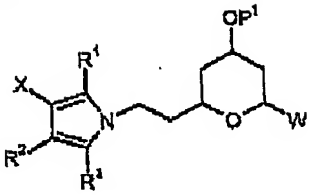
b) reducing the compound of formula (2) to give a compound of formula (3):



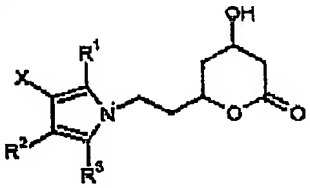
c) coupling the compound of formula (3) with a compound of formula (4):



to give a compound of formula (5):

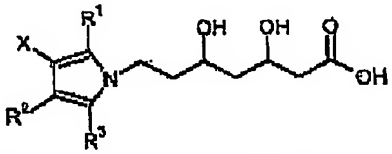


d) when W represents $-OP^2$, deprotecting and then oxidising the compound of formula (5) to give a compound of formula (6):



and

e) subjecting the compound of formula (5) when W represents =O, or compound of formula (6) to ring-opening, and removal of any remaining protecting groups, to give a compound of formula (7):



Protecting groups which may be represented by P^1 and P^2 include alcohol protecting groups, examples of which are well known in the art. Particular examples include tetrahydropyranyl, benzyl and methyl groups. Preferred protecting groups are silyl groups, for example triaryl- and especially trialkylsilyl groups. Especially preferred examples are trimethylsilyl, t-butyldimethylsilyl and t-butyldiphenylsilyl groups.

Protecting groups which may be represented by P^1 and P^2 may be the same or different. When the protecting groups P^1 and P^2 are different, advantageously this may allow for the selective removal of only P^1 or P^2. Preferably, when the protecting groups P^1 and P^2 are different, P^1 is a silyl group and P^2 is a methyl group.

Cyanation of compounds of formula (1) can be achieved by methods known in the art for displacing a halo group with a cyanide. Preferably, the process comprises contacting the compound of formula (1) with a source of cyanide. Preferred sources of cyanide include cyanide salts, especially ammonium or alkali metal cyanides, particularly sodium or potassium cyanide. A particularly preferred process comprises contacting the

compound of formula (1) with 5 molar equivalents of KCN in the presence of dimethylsulfoxide solvent at a temperature of, for example, about 50°C.

Reduction of compounds of formula (2) can be achieved using reduction systems known in the art for the reduction of nitrile groups. Preferred examples include reduction with Raney nickel and hydrogen or with hydrogen in the presence of a catalyst, such as palladium on carbon. When palladium on carbon catalysed hydrogenation is employed, preferred conditions comprise the use of methanol solvent at elevated temperature, such as about 40°C, in the presence of from about 0.01 to 100 molar equivalents of ammonia.

The coupling of the compound of formula (3) with the compound of formula (4) may employ conditions analogous to those given in WO89/07598 for the corresponding coupling. The conditions preferably comprise refluxing the compounds of formula (3) and (4) in a hydrocarbon solvent, such as toluene or cyclohexane, or mixtures thereof, followed by contact with aqueous acid, such as aqueous HCl.

When W represents OP^2, the protecting group may be removed to form a hydroxy group by methods known in the art for the removal of the given protecting group. For example, silyl protecting groups may be removed by contact with a source of fluoride ion, such as tetrabutylammonium fluoride.

Oxidation of compounds formed by deprotection of compounds wherein W represents $-OP^2$ may employ conditions known in the art for the oxidation of pyranols to pyranones, and include those given in "Comprehensive Organic Transformations", R.C. Larock, 2nd Ed (1999) p 1670, published by Wiley VCH, incorporated herein by reference. Preferred oxidation systems include Ag_2CO_3/Celite, especially Celite J2, or bromine.

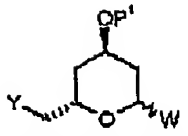
Ring opening of the compounds of formula (5), when W represent =O or formula (6) may employ conditions known in the art for ring opening of a pyranone. Preferably, the ring is opened by contact with a base, such as sodium hydroxide. Methanol is conveniently employed as solvent.

Remaining protecting groups may be removed by methods known in the art for the removal of the given protecting group. For example, silyl protecting groups may be removed by contact with a source of fluoride ion, such as tetrabutylammonium fluoride.

It will be recognised that when X represents a group of formula $-COOR^4$, this may be converted to a group wherein X represents $-CONR^5R^6$ at any stage during the process, for example by reaction of the corresponding compounds of formulae (2), (3), (4), (5), (6) or (7) with a compound of formula HNR^5R^6.

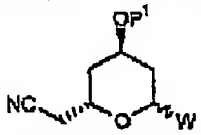
It will also be recognised that compounds of formulae (2), (3) and (4) may also be subjected to oxidation (when W represents –OH) or deprotection and oxidation (when W represents (-O-protecting group) to form the corresponding compound wherein W represents =O.

Preferred compounds of formula (1) are compounds of formula:



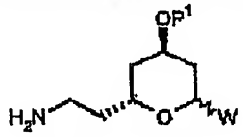
wherein W, P^1 and Y are as previously described.

Preferred compounds of formula (2) are compounds of formula:



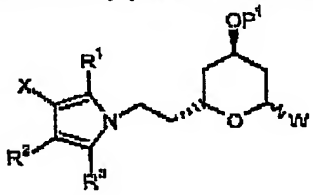
wherein W and P^1 are as previously described.

Preferred compounds of formula (3) are compounds of formula:



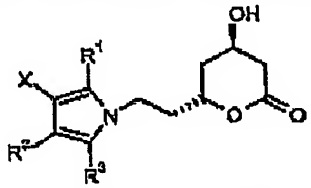
wherein W and P^1 are as previously described.

Preferred compounds of formula (5) are of formula:



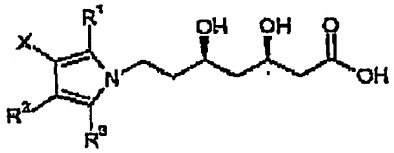
wherein R^1, R^2, R^3, W, X and P^1 are as previously described.

Preferred compounds of formula (6) are of formula:



wherein R^1, R^2, R^3, and X are as previously described.

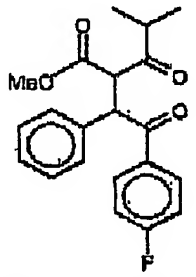
Preferred compounds of formula (7) are of formula:



wherein R^1, R^2, R^3, and X are as previously described.

Compounds of formula (7) are advantageously converted to pharmaceutically acceptable salts, especially their calcium salts.

Compounds of formula (4) are advantageously prepared by the methods given in J. Med. Chem., 1991, 34, pp357-366. Particularly preferred compounds of formula (4) are compounds of formula:



Compounds of formula (1) are advantageously prepared by enzyme catalysed condensation of acetaldehyde and 2-haloacetaldehyde, for example using the method given in US patent 5,795,749.

Compounds of formulae (2) and (3) and, when W is OP^2, formula (5) form further aspects of the present invention.

The invention is illustrated by the following Examples.

Example 1 - Deprotection of a compound of Formula (5) where R^1= iPr , R^2= Ph, R^3= 4-FC_6H_4, X= C(O)NHPh , P^1=$SiEt_3$, W=OP^2 where P^2=H

A compound of Formula (5) [where R^1= iPr , R^2= Ph, R^3= 4-FC_6H_4, X= C(O)NHPh, P^1=$SiEt_3$, W=OP^2 where P^2=H] (100mg) was dissolved in anhydrous THF. HF.pyridine was added (0,1ml) at 0°C and allowed to warm to room temperature. The mass was quenched with ether/and sodium bicarbonate solution. The phases separated and the aqueous phase back extracted with ether. The organic phases were combined, dried and evaporated to produce and oil (75mg).

Example 2 - Preparation of a compound of Formula (6) where R^1= iPr , R^2= Ph, R^3= 4-FC_6H_4, X= C(O)NHPh , P^1=H

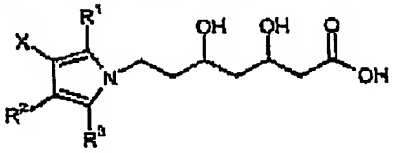
The compound from Example 1 (35mg, 0.065mmol) in dichloromethane (0.5ml) was added to Dess-Martin periodinane (30mg, 0,07mmol) and stirred at room temperature for 2.5 hours. The reaction was partitioned between 1M sodium hydroxide and diethyl ether. The phases were then separated and the organic volume reduced in vaccuo to afford the crude product oil.

^{1}H 500MHz CDCl3: 9.8, 7.5, 7.28, 7.2, 7.08, 7.02, 6.98, 5.2, 4.6, 4.1, 4.0, 3.9, 3.2, 2.6, 2.4, 1.8, 1.4.

^{13}C 125.72MHz DMSO: 169.6, 165.9, 139.3, 135.9, 134.7, 133.3, 129.4, 128.8, 128.4, 127.5, 127.2, 125.3, 122.9, 120.7, 119.3, 117.6, 115.4, 25.5, 22.1, 22.3, 39.5, 34.5, 72.8, 36.8, 61.0, 38.3.

CLAIMS

1. A process for the preparation of a compound of formula (7):



wherein

R^1 represents an alkyl group, such as a C_{1-6} alkyl group, and preferably an isopropyl group;

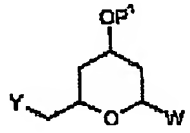
R^2 represents an aryl group, preferably a phenyl group

R^3 represents an aryl group, preferably a 4-fluorophenyl group

X a group of formula –COZ, wherein Z represents $-OR^4$, in which R^4 represents an alkyl, preferably a methyl or ethyl, group, or $-NR^5R^6$, wherein R^5 and R^6 each independently represent H, alkyl, or aryl, and preferably R^5 is H and R^6 is phenyl

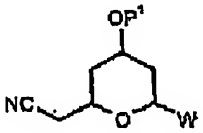
which comprises

a) cyanating a compound of formula (1):

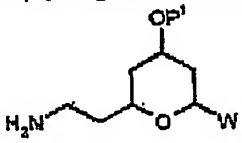


wherein Y represents a halo group, preferably Cl or Br; P^1 represents hydrogen or a protecting group, and W represents =O or $-OP^2$, in which P^2 represents hydrogen or a protecting group,

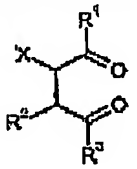
to give a compound of formula (2):



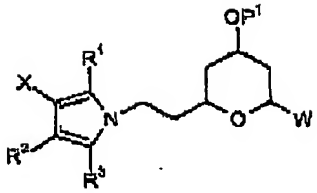
b) reducing the compound of formula (2) to give a compound of formula (3):



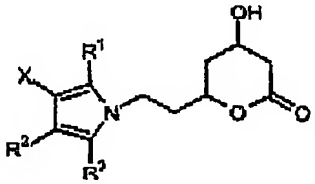
c) coupling the compound of formula (3) with a compound of formula (4):



to give a compound of formula (5):

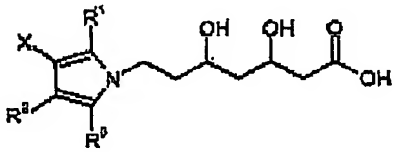


d) when W represents $-OP^2$, deprotecting and then oxidising the compound of formula (5) to give a compound of formula (6):

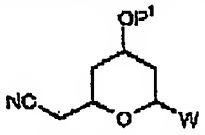


and

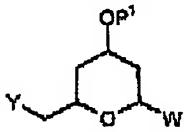
e) subjecting the compound of formula (5) when W represents =O, or compound of formula (6) to ring-opening, and removal of any remaining protecting groups, to give a compound of formula (7):



2. A process for the preparation of a compound of formula (2):

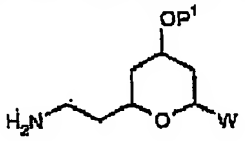


which comprises cyanating a compound of formula (1):

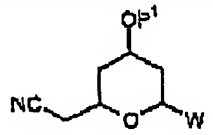


wherein Y represents a halo group, preferably Cl or Br; P^1 represents hydrogen or a protecting group, and W represents =O or $-OP^2$, in which P^2 represents hydrogen or a protecting group.

3. A process for the preparation of a compound of formula (3):

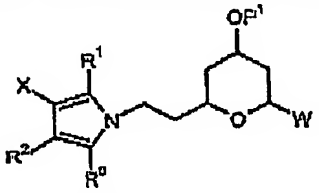


which comprises reduction of a compound of formula (2):

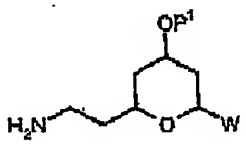


wherein P^1 represents hydrogen or a protecting group, and W represents =O or $-OP^2$, in which P^2 represents hydrogen or a protecting group.

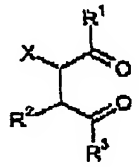
4. A process for the preparation of a compound of formula (5):



which comprises coupling the compound of formula (3):



with a compound of formula (4):



wherein

R^1 represents an alkyl group, such as a C_{1-6} alkyl group, and preferably an isopropyl group;

R^2 represents an aryl group, preferably a phenyl group;

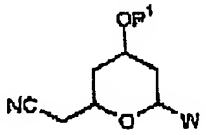
R^3 represents an aryl group, preferably a 4-fluorophenyl group;

X a group of formula $-COZ$, wherein Z represents $-OR^4$, in which R^4 represents an alkyl, preferably a methyl or ethyl, group, or $-NR^5R^6$, wherein R^5 and R^6 each independently represent H, alkyl, or aryl, and preferably R^5 is H and R^6 is phenyl;

P^1 represents hydrogen or a protecting group; and

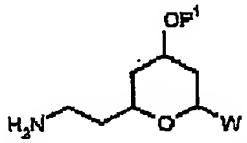
W represents =O or $-OP^2$, in which P^2 represents hydrogen or a protecting group.

5. A compound of formula (2):



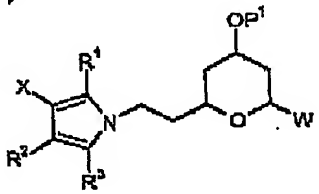
wherein P^1 represents hydrogen or a protecting group, and W represents =O or $-OP^2$, in which P^2 represents hydrogen or a protecting group.

6. A compound of formula (3):



wherein P^1 represents hydrogen or a protecting group, and W represents =O or $-OP^2$, in which P^2 represents hydrogen or a protecting group.

7. A compound of formula (5):



wherein,

R^1 represents an alkyl group, such as a C_{1-6} alkyl group, and preferably an isopropyl group;

R^2 represents an aryl group, preferably a phenyl group;

R^3 represents an aryl group, preferably a 4-fluorophenyl group;

X a group of formula $-COZ$, wherein Z represents $-OR^4$, in which R^4 represents an alkyl, preferably a methyl or ethyl, group, or $-NR^5R^6$, wherein R^5 and R^6 each independently represent H, alkyl, or aryl, and preferably R^5 is H and R^6 is phenyl;

P^1 represents hydrogen or a protecting group; and

W represents $-OP^2$, in which P^2 represents hydrogen or a protecting group.